Role of \(^{18}\text{F-FDG-PET}\) imaging in the diagnosis of autoimmune encephalitis

Establishing the clinical diagnosis of autoimmune encephalitis can be challenging as patients present with various unspecific symptoms.\(^1\) In a Position Paper\(^1\) in The Lancet Neurology, Francesc Graus and colleagues proposed an initial diagnostic work-up relying on conventional neurological evaluation and standard diagnostic tests such as MRI, CSF sampling, and EEG. This approach would enable clinicians to make a timely diagnosis of “possible autoimmune encephalitis”, allowing initiation of immunotherapy. In a second step, the authors proposed comprehensive antibody testing to help to establish a diagnosis of “probable autoimmune encephalitis” or “definite autoimmune encephalitis”, potentially enabling refinement of treatment.\(^1\)

With regards to brain imaging, the proposed diagnostic framework solely relies on MRI. However, as acknowledged by Graus and colleagues,\(^1\) limbic encephalitis is known to occur in a relevant fraction of patients with normal or non-specific MRI findings.\(^2\) In limbic encephalitis, \(^{18}\text{fluorodeoxyglucose (^{18}F-FDG) PET imaging}\) has been reported to typically reveal medial temporal lobe hypermetabolism even in MRI-negative or inconclusive cases, suggesting that it could be more sensitive than MRI (figure).\(^2\) In the Position Paper\(^1\) by Graus and colleagues, this important evidence is mentioned only as a footnote in panel 2.

Although we commend the Position Paper,\(^1\) we suggest a stronger consideration of \(^{18}\text{F-FDG-PET imaging}\) in supporting the diagnosis of autoimmune encephalitis. This proposal is also supported by results of one of the largest multimodal neuroimaging case series\(^2\) in limbic encephalitis, which demonstrated that \(^{18}\text{F-FDG-PET imaging}\) might even have a diagnostic role in patients with autoantibody-negative limbic encephalitis. Furthermore, the differences in PET-based glucose metabolism patterns in such patients support the existence of limbic encephalitis subtypes associated with antibodies that are yet to be identified.\(^1\)

Apart from the stated potential of \(^{18}\text{F-FDG-PET imaging}\) for improved early diagnosis of limbic encephalitis, we propose the following scenarios in which diagnoses of autoimmune encephalitis could be supported in the future by this molecular imaging approach.

First, in limbic encephalitis and in other autoimmune encephalitis subtypes \(^{18}\text{F-FDG-PET imaging}\) also shows, in a relevant number of patients, extra-limbic metabolic abnormalities (mainly in the brainstem, cerebellum, or cerebral cortex). These PET findings were associated with clinical symptoms and active disease status more strongly than the MRI findings.\(^3\) Thus, \(^{18}\text{F-FDG-PET imaging}\) has the potential to improve estimation of disease severity in patients with autoimmune encephalitis, with implications for follow-up evaluation and therapy monitoring.\(^4\)

Second, in the future, \(^{18}\text{F-FDG-PET imaging}\) might have a role in the diagnosis of anti-NMDA receptor encephalitis, an entity for which MRI has poor sensitivity.\(^5\) Several \(^{18}\text{F-FDG-PET imaging studies}\) in these patients have shown metabolic abnormalities in different brain areas, including the frontal, temporal, and occipital lobes, and the basal ganglia, cerebellum, and brainstem.\(^6\) Again, the PET findings were more clearly associated with the clinical picture (ie, basal ganglia involvement and presence of movement disorders), disease severity, and recovery after therapy than the MRI findings.\(^5\)

Finally, on a practical note, \(^{18}\text{F-FDG-PET imaging}\) is an attractive future addition to the proposed work-up for two reasons. First, whole-body \(^{18}\text{F-FDG-PET imaging}\) is often done in patients with paraneoplastic syndromes to screen for malignancy. Such whole-body imaging can easily be extended to cover the brain without increases in radiation burden. Second, in the past few years, with the introduction of combined PET and MRI systems, many groups have already started to replace MRI with PET-MRI in the diagnostic algorithm for other brain disorders.\(^7\)

We encourage feasibility studies for the use of this method in autoimmune encephalitis.

We agree that, as a next step, the proposed diagnostic framework for autoimmune encephalitis needs to be tested in clinical practice.\(^2\) Further testing can also provide an opportunity to assess the contribution of \(^{18}\text{F-FDG-PET imaging}\) in the scenarios discussed here. In parallel, the imaging community needs to refine standard procedures for acquisition and reading of PET imaging data in autoimmune encephalitis, and to confirm the results in large prospective studies.

We declare no competing interests.

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Authors’ reply

We thank Silvia Morbelli and colleagues for their comments on the role of brain 18fluorodeoxyglucose (18F-FDG) PET imaging in the management of autoimmune encephalitis. We agree about the potential use of 18F-FDG-PET in the diagnosis and evaluation of the response to immunotherapy in autoimmune encephalitides.1 However, two reasons led us to downplay the role of 18F-FDG-PET imaging in our Position Paper.2 First, this technique remains unavailable in many hospitals and rarely can be obtained on an emergency basis. As indicated, the main goal of our Position Paper3 was to increase confidence in the diagnosis of autoimmune encephalitis with conventional neurological evaluation and standard diagnostic tests (eg, MRI, CSF, or EEG) that are available in most hospitals during the first 48 h of the clinical evaluation. This early assessment is necessary to enable initiation of immunotherapy without delay, which is crucial to improve patient outcomes.4

Second, 18F-FDG-PET is still a relatively new imaging method and further studies are needed to validate its positive and negative predictive value for the diagnosis of autoimmune encephalitis. Many types of autoimmune encephalitides exist, and these represent a small percentage of all types of infectious and non-infectious encephalitides, all of which are frequently associated with seizures. In addition to inflammation and seizures, the effects of the antibodies might also alter the metabolic findings on PET imaging. For example, 18F-FDG-PET imaging findings in patients with anti-NMDA receptor encephalitis have been suggested to vary over the course of the disease, resembling those caused by antagonists of the NMDA receptor, such as ketamine.4 However, for initial evaluation of this and other types of autoimmune encephalitis, brain 18F-FDG-PET imaging has low specificity regarding the cause of the disorder.5 Similar limitations apply for the use of 18F-FDG-PET in other CNS disorders. For example, despite the extensive literature on 18F-FDG-PET in gliomas, this technique has not been incorporated into most widely accepted criteria to assess the effects of therapy, and it is pending validation in clinical trials to ensure standardisation in routine clinical practice.6

In autoimmune encephalitis, the low frequency of the disorder makes achieving this goal even more problematic. A possible way to overcome this limitation would be through a collaborative effort to report findings from 18F-FDG-PET imaging studies in a central database to collect information on the metabolic patterns of the different types of autoimmune encephalitis.

FG has received licensing fees from Euroimmun for the use of IgLON5 as a diagnostic test. JD receives royalties from Athena Diagnostics for a patent for the use of Ma2 as an autoantibody test; royalties from Euroimmun for the use of NMDAR and GABABR1 as autoantibody tests; and licensing fees from Euroimmun for the use of DPPX, GABA receptor, and IgLON5 antibodies as diagnostic tests. JD has also received unrestricted research grants from Euroimmun and the CELLEX Foundation.

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